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macrophage colony stimulating factor (M-CSF), Flt-3 ligand and tumor necrosis factor (TNF) alpha.

38. (Once Amended) A mucin antigen delivery vehicle, comprising an isolated mannose receptor-bearing cell and a conjugate comprising mucin antigen and a carbohydrate polymer comprising mannose selected from the group consisting of fully oxidized mannose comprising free aldehydes and partially reduced mannose having aldehydes.

43. (Once Amended) The method of Claim 39, wherein said antigen delivery medium comprises a conjugate comprising mucin antigen and a carbohydrate polymer comprising mannose selected from the group consisting of fully oxidized mannose comprising free aldehydes and partially reduced mannose having aldehydes.

49. (Once Amended) The method of Claim 48, wherein said biological response modifier is selected from the group consisting of granulocyte macrophage colony stimulating factor (GM-CSF), interleukin-3, interleukin-4, vitamin D, [GM-CSF,] macrophage colony stimulating factor (M-CSF), Flt-3 ligand and tumor necrosis factor (TNF) alpha.

REMARKS

Priority Claim:

The Examiner has indicated that the status of the priority documents be updated. Applicants have amended the specification to update the reference to the earlier filed applications.

Objection to the Specification and Rejection of Claims 13-16 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 13-16 under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner contends that the specification is enabling for mannan conjugated to human mucin (i.e., an antigen), but does not reasonably provide enablement for conjugates comprised of fragments of mucin. The Examiner asserts that the specification has not taught the selection of appropriate fragments or the characteristics of fragments with sufficient clarity to allow a person of ordinary skill in the art to identify them.

Initially, Applicants note that Claim 13 has been amended to clarify the term fragment by reciting that the fragment is at least 5 amino acids in length and is antigenic. Support for these

amendments is found, for example, on page 22, lines 4-14, and on page 25, line 20, through page 26, line 6, of the specification.

With regard to the Examiner's contention that one of skill in the art would not be enabled to select the appropriate fragments or know the characteristics of fragments suitable for use in the claimed composition, Applicants traverse the Examiner's position and submit that the specification provides sufficient detail regarding the claimed fragments, including specific examples of such fragments. For example, the passage bridging pages 3-4 provides repeated (VNTR) regions of MUC 1 to MUC7, on which antigenic fragments could be based. Furthermore, the paragraph bridging pages 25-26 also provide clear examples of fragments of mucin that could be used in accordance with the present invention. In addition, given the teachings of the present specification, a skilled artisan could use an algorithm based search or an epitope prediction computer program to select putative immunogenic peptides for testing. Examples of such programs, available at the time of the present invention, may be found in:

Devenport MP *et al* "An empirical method for the prediction of T-cell epitopes", *Immunogenetics* 42:392, 1995,

Rammensee H-G *et al* "MHC ligands and peptide motives", Landes Bioscience, Autstin, Texas, USA 1997 or

on website bimas.dcrt.nih.gov/molbio/hla_bind/.

Finally, the specification, in combination with the level of skill in the art, provides sufficient guidance to the skilled artisan to determine whether a given peptide fragment is antigenic, and in particular, whether such fragment can bind to MHC and in this context, elicit a cellular immune response. See, for example, page 16, line 7-21; page 41, line 5, through page 43, line 7; Example 1. More particularly, it would not require undue experimentation to test the effectiveness of a given fragment of an antigen, as Example 1 provides guidance on how cellular immune responses to the composition of the invention can be measured. For example, a skilled artisan would decide on a fragment to be tested, prepare a fusion protein as taught at page 44 lines 5–8, and test the composition for cellular immunogenicity in accordance with the method set forth in Example 1.

In view of the foregoing amendments and remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 13-16 under 35 U.S.C. § 112, first paragraph.

Objection to the Specification and Rejection of Claims 1, 3-21, 23-34, 36-45 and 47-51 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 1, 3-21, 23-34, 36-45 and 47-51 under 35 U.S.C. § 112, first paragraph. The Examiner asserts that the specification is enabling for mannan conjugated to an antigen, but not for conjugates comprised of mannose or oxidized forms thereof. The Examiner contends that the specification discloses the carbohydrate polymer mannan in the specific examples, but that the specification does not teach the use of any other carbohydrates. Moreover, the Examiner notes that mannose is a monosaccharide containing a single sugar moiety and that mannan is a polymer of mannose units. The Examiner asserts that it is not clear that the terms mannose and mannan are being used interchangeably, and that it is not certain that a single mannose would possess the same properties as the mannan for use in the claimed invention.

In response to the Examiner's rejection, Applicants first note that independent Claims 1 and 27 have been amended to more clearly recite a carbohydrate polymer comprising mannose, which clarifies that carbohydrate polymers, and not a single mannose, are being claimed. Support for this amendment is found in the specification in the paragraph bridging pages 27-28, which provides basis for a carbohydrate polymer, including polymers comprising mannose. Lines 13-16 of page 29 disclose polymers comprising oxidized mannose that comprises free aldehydes. Page 27, line 16, through page 32, line 9, and Examples 1 and 2 provide details regarding the composition of the polymer, how to obtain carbohydrates, and how to make the carbohydrate polymer-antigen conjugate. As set forth on page 29, lines 7-13, Applicants note that one important aspect of the present invention is the conjugation of the antigen to an oxidized carbohydrate in which there are exposed or free aldehyde groups, such that delivery of the antigen to the antigen presenting cell is enhanced. Moreover, the inclusion of mannose subunits in the polymer (e.g., mannan), in addition to being a carrier for the antigen, allows the conjugate to bind to and be internalized, processed and presented by a mannose-receptor bearing cell of the present invention. Applicants have taught one of skill in the art how to make and use a conjugate having these characteristics. Therefore, the specification has provided sufficient guidance to enable one of skill in the art to make and use the present invention, without undue experimentation.

In view of the foregoing amendments and remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3-21, 23-34, 36-45 and 47-51 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 11, 12 and 25[sic] Under 35 U.S.C. § 112, Second Paragraph:

The Examiner has rejected Claims 11, 12 and 25[sic] under 35 U.S.C. § 112, second paragraph. The Examiner contends that these claims are vague and indefinite in the recitation of several abbreviations, and states that the abbreviations should be spelled out upon their first appearance. Applicants have amended Claims 11, 12 and 25, as well as Claims 34 and 49 to spell out the names of the abbreviated compounds. Support for these amendments is found in the specification on page 18, lines 9-20; page 22, line 15, through page 23, line 20; and page 24, lines 4-7.

The Examiner has also rejected Claim 12, asserting that this claim is confusing in the recitation of "amino acid subunit" of an antigen, contending that this term implies a portion of a single amino acid. Applicants have amended Claim 12 to remove the term found objectionable by the Examiner and to instead recite "an antigenic fragment" of the antigen that is 5 or more amino acids in length. Support for this amendment is found in the specification on page 21, line 19, through page 22, line 14.

In view of the foregoing amendments and remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 11, 12 and 25 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 1, 3-15, 17-21, 23-27, 32-34, 36-40, 43-45 and 47-50 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1, 3-15, 17-21, 23-27, 32-34, 36-40, 43-45 and 47-50 under 35 U.S.C. § 103, contending that these claims are unpatentable over Rodwell et al., in view of Edelsen et al. and in further view of Kjeldsen et al. Specifically, the Examiner contends that Kjeldsen et al. teach the administration of high molecular weight glycoproteins isolated from human lung squamous cell carcinoma lines where the glycoproteins comprise the Tn antigen, which is allegedly a mucin antigen. The Examiner contends that the glycoproteins are a conjugate between an antigen and a carbohydrate polymer, and asserts that the glycoproteins appear to be MUC1. The Examiner notes that since the Patent Office does not have the facilities to compare the claimed

conjugate with the conjugate of the prior art, the burden is upon Applicants to show a novel or nonobvious difference between the claimed product and the product of the prior art. The reference of Rodwell et al. is cited for allegedly teaching the oxidation of mannose to form aldehydes, followed by the reaction of oxidized mannose with free amine groups on proteins. The Examiner contends that Rodwell et al. teach that oxidation of carbohydrate significantly increases the number of sites for coupling compounds. The Examiner admits that the combination of Kjeldsen et al. and Rodwell et al. do not teach immunoregulatory compositions further comprised of mannose receptor-bearing cells treated with cytokines, but cites the reference of Edelsen et al. as allegedly teaching compositions comprising macrophages to be used as cellular vaccines. Therefore, the Examiner contends that it would be obvious to combine the teachings of Rodwell et al., Kjeldsen et al. and Edelsen et al. to form the claimed immunoregulatory composition. The Examiner submits that one of skill in the art would have been motivated to combine the references in view of the potential advantages of enhanced immunogenicity of an antigen in a cellular vaccine.

Applicants traverse the Examiner's rejection under 35 U.S.C. § 103. Initially, it is noted that the present claims are directed to immunoregulatory compositions comprising mannose-receptor bearing cells and a conjugate of a carbohydrate polymer comprising oxidized mannose and an antigen. These immunoregulatory compositions are capable of enhancing T cell responses upon administration to a subject, as indicated at page 5 lines 19-23. Applicants submit that the combination of references cited by the Examiner does not teach or suggest the claimed invention.

With regard to the reference of Rodwell et al., this reference describes *antibodies* that are improved in that they possess specific binding sites for other compounds. The binding sites are carbohydrate side chains attached to the antibodies at the *non-antigen binding region*, and are created by using a "dolichol-dependent, asparagine-linked pathway", as disclosed at column 1 lines 24-26. Compounds may then be bound to the modified antibodies via the carbohydrate side chains. A list of possible compounds is given at column 3 lines 47-68, and it is noted that no antigens or mucin polypeptides are given. As stated in column 2, lines 47-50, the antibody-mannose-compound functions as an *antibody linker*, linking an active agent (the compound) to the antibody via the mannose site. Thus, the teachings of Rodwell et al. are: a) antibodies and b) carbohydrate side chains attached to regions that do not partake in antigen binding. These are not elements of the present invention. Indeed, no preformed antibodies with carbohydrate side chains are required or

claimed in the present invention; such antibodies are neither structurally nor functionally equivalent to the claimed conjugate. Thus, the Rodwell citation does not teach the invention claimed, which uses a mannose-containing polymer for targeting antigens to mannose receptor bearing cells such as macrophages, and for specifically inducing mannose receptor bearing cells such as macrophages to present the antigens to T cells for generating immune responses.

Furthermore, the aim of Rodwell et al. to make improved antibodies is different from the aim of the present invention, which is to obtain a product (obtained via a mannose receptor-bearing cell and carbohydrate-antigen conjugate) to enhance T cell responses. A skilled artisan interested in the latter would not be motivated to follow the teachings of Rodwell et al., as preformed antibodies function in a different way to compositions having the ability to mount a T cell immune response upon administration to a subject. More specifically, modified antibodies function in a different way to antigens conjugated to carbohydrate polymers, since the conjugate will have to stimulate a cellular immune response whereas antibodies form part of a humoral immune response (e.g., are ready to act on pathogens without processing). Hence, there is no motivation to regard this citation as relevant to the invention claimed.

With regard to the reference of Kjeldsen et al., Applicants submit that this reference does not make up for the deficiencies of Rodwell et al. Kjeldsen et al. describes improved methods of producing monoclonal antibodies against mucin-type glycoproteins (See the abstract). At column 1 lines 26-27, it is stated that the new method avoids a number of extra steps as compared to conventional methods. This document does not relate to the elicitation of cellular immune responses. The immunogens used by Kjeldsen et al. are core structures of mucin-type glycoproteins, such as T-antigen and Tn-antigen described at column 7 lines 26-55. As can be noted from the disclosure of Kjeldsen et al., the immunogens are glycoproteins having GalNAc residues linked to the hydroxyl groups of amino acid residues in the peptide chain. In contrast, antigens useful in accordance with the present invention include mucin polypeptides or in a preferred embodiment, peptides comprising repeated subunits thereof (VNTR) as indicated at pages 3-4 and page 26 lines 1-3. Furthermore, the antigens of the present invention are linked to a carbohydrate polymer comprising oxidized mannose (e.g., mannan) via the amino group, not to a sugar molecule via the hydroxyl group, as taught by Kjeldsen et al. (See page 30 lines 5-8 and figure 14 of the present specification). The antigens of Kjeldsen et al. differ in stoichiometry to the conjugates in accordance

with the invention claimed. Therefore, Kjeldsen et al. teaches improved methods of generating antibodies to antigens that are *structurally different* from the antigens conjugated to the carbohydrate polymer in accordance with the present invention. Thus, the citation does not teach the elements of the invention claimed.

The citation also does not teach that the use of the T or Tn antigens would enhance T cell responses. Therefore, Kjeldsen et al. provides no motivation to a skilled artisan to regard it as relevant to the present invention. Kjeldsen *et al* describes an improved method of making antibodies, and is not directed to T cells and T cell responses. Hence, there would be no incentive for a skilled artisan to regard this document as relevant, and combine it with the other citations.

With regard to the teachings of Edelsen et al., this citation also does not make up for the deficiencies of Rodwell et al. and Kjeldsen et al. Edelsen et al. describe methods and compositions for improving the effectiveness of *radiation* therapy (See the abstract). Edelsen et al. teach a combination of antigens isolated after irradiation of solid tumors, and "contacting" these with cellular preparations. The cells (e.g. leukocytes) have been "altered" or damaged by photopheresis or photoinactivation (see column 2 lines 1-2 and column lines 33-35). These elements are not present in the claimed invention, and in fact, damaging the mannose receptor-bearing cells by photoinactivation would be expected to lead to an ineffective immunoregulatory composition. Thus, Edelsen et al. can be viewed as a *teaching away* from the present invention. Furthermore, the document does not disclose or allude to the use of carbohydrate polymer-antigen conjugates. Accordingly, the citation, alone or in combination with Rodwell et al. and Kjeldsen et al., fails to teach the elements of the present invention. Moreover, there would be no motivation for a skilled artisan to regard the citation of Edelsen et al. as relevant to the invention as claimed. As discussed above, Edelson *et al* teaches leukocytes that must first be damaged by photoinactivation, before contacting them with antigens isolated from irradiated solid tumors, to form a composition that is used to improve radiation therapy. It is expected that treatment of mannose-receptor bearing cells in this way will result in eradication of the cells, and consequently, the inability to obtain the immuno-regulatory compositions of the invention.

In summary, Applicants submit that the documents cited by the Examiner do not render the invention claimed obvious. As set forth above, none of the cited references, alone or in combination, teach or suggest immunoregulatory compositions comprising mannose-receptor bearing cells and

a conjugate of a carbohydrate polymer comprising oxidized mannose and an antigen. At best, a combination of the teachings cited by the Examiner would provide: mucin glycosylated peptide antigens wherein hydroxyl groups of amino acid residues are linked to a sugar molecule; leukocytes that have been damaged by photoinactivation; and antibodies with carbohydrate side chains at sites not involved in antigen binding, with no motivation provided by any of the references to make even that combination of elements.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3-15, 17-21, 23-27, 32-34, 36-40, 43-45 and 47-50 under 35 U.S.C. § 103.

Rejection of Claims 1, 3-21, 23-27, 32-34, 36-40, 43-45, and 47-50 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 3-21, 23-27, 32-34, 36-40, 43-45, and 47-50 under 35 U.S.C. § 103, contending that these claims are unpatentable over Taylor-Papadimitriou et al. in view of Rodwell et al. and in further view of Edelsen et al. Specifically, Taylor-Papadimitriou et al. is alleged to teach peptides derived from human polymorphic endothelial mucin and their use in immunization. The Examiner contends that the reference teaches the preparation of these peptides as a fusion protein and the conjugation of these peptides to one or more saccharide moieties. The Examiner admits that Taylor-Papadimitriou do not teach conjugation of the peptides to oxidized mannose or a composition comprising mannose receptor-bearing cells stimulated with cytokines. The Examiner asserts that the teachings of Rodwell et al. and Edelsen et al, as discussed in the rejection above, provide the remaining teachings. The Examiner contends that it would have been obvious in view of this combination of references to form the claimed immunoregulatory composition, the motivation being the potential advantages of enhanced immunogenicity of an antigen in a cellular vaccine.

Applicants traverse the Examiner's rejection under 35 U.S.C. § 103. Applicants refer to the discussion of Rodwell et al. and Edelsen et al. above and again submit that neither of these references, alone or in combination, teach or suggest the immunoregulatory composition of the present invention, comprising mannose-receptor bearing cells and a conjugate of a carbohydrate polymer comprising oxidized mannose and an antigen. Applicants further submit that Taylor-Papadimitriou et al. do not make up for the deficiencies of the combination of Rodwell et al. and Edelsen et al. Taylor-Papdimitriou et al. teach peptides derived from human polymorphic epithelial

mucin. As the Examiner admits, Taylor-Papadimitriou et al. do not teach conjugation of the peptides to oxidized mannose, nor of a composition comprising mannose receptor-bearing cells. As already indicated above, none of Rodwell or Edelson provides any motivation to regard either reference as relevant to the present invention and indeed, neither reference teaches the elements presently claimed. The teaching of a peptide by Taylor-Papadimitriou et al. does not teach or suggest to the skilled artisan to combine or modify a teaching of leukocytes that have been damaged by photoinactivation or of antibodies with carbohydrate side chains at sites not involved in antigen binding to arrive at the present invention. Accordingly, there would be no motivation to make the combination of references as the Examiner has done.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 3-21, 23-27, 32-34, 36-40, 43-45, and 47-50 under 35 U.S.C. § 103.

Applicants have attempted to address the Examiner's concerns as set forth in the July 28 Office Action. In the event that the Examiner has any questions or concerns regarding Applicants' position, the Examiner is invited to contact the below named agent at (303) 863-9700.

Respectfully submitted,

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